Key biomarker's new role in head and neck cancer

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Researchers at UNC have proposed a novel interpretation of an old biomarker which, if validated, could fundamentally transform the management of head and neck cancer.

Dr. Hayes is senior author of the study.

In a study released online in the British Journal of Cancer this week, investigators at UNC showed that when correctly interpreted, the marker – tumor suppressor gene p16- can have either strongly favorable or, paradoxically, strongly unfavorable prognostic implications. The favorable association with p16 previously had been widely recognized. The potential to characterize a large number of head and neck tumors in an unfavorable way is completely novel.

Neil Hayes, MD, MPH, and study senior author, says, "If we are able to repeat this observation in a validation cohort, I expect that this biomarker will change the way we manage patients with head and neck squamous cancers." Dr. Hayes is a member of UNC Lineberger Comprehensive Cancer Center.

The story starts with the human papilloma virus (HPV). Over the last five years the importance of HPV infection in head and neck cancer has ignited a firestorm of interest. A consensus has emerged that patients with HPV-associated tumors have substantially improved survival, and may have different responses to therapy. However, the story is not so simple.

Testing for HPV is complex and the diagnostic performance of all known markers has been disappointing. For example, many patients expected to be positive/elevated for HPV demonstrate a negative test. Likewise, some patients who test positively and have significant smoking histories fail to show the improved outcomes associated with the virus.

Accordingly, a second marker has gained considerable interest, that of the tumor suppressor gene p16. P16 is nearly always elevated in patients who are HPV positive and appears to have some favorable properties when used in the clinic relative to the direct tests for HPV. Unfortunately while p16 testing appears to address some shortcomings of direct HPV testing, many questions remain. Most importantly, the biomarker is only predictive when considered in a limited set of patients, primarily those with tonsil cancer and in those who have very limited smoking histories.

In experiments, Hayes and colleagues proposed a method of p16 evaluation that appears to strikingly segregate the groups of high p16, separating those with good prognosis from those with poor prognosis. In the process, the investigators extend the use of the biomarker from the minority of patients with tonsil cancers to a much broader group of patients with a wide variety of tumors of the head and neck. At the same time, the new evaluation appears to clarify the role of smoking in interpretation of the biomarker.

Hayes and colleagues were puzzled, however, by an interesting paradox. In addition to HPV infection, other patients demonstrated elevated p16 expression, but did not have HPV infection. These patients tended to have much more dangerous primary tumor alterations such as mutation of the gene retinoblastoma 1 (RB1). Unlike HPV infected patients, these patients were generally felt to have a very unfavorable prognosis.

In short, in patients with tonsil cancers likely to have HPV, p16 was a favorable marker, yet in other cases where HPV

infection was less likely, high p16 might either be associated with the favorable HPV infection or the unfavorable RB1 mutation. Likewise, presumably some patients with high p16 in the tonsil could also have the unfavorable RB1 mutation and falsely be assumed to be low risk where in fact the opposite was true.

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